15. MISCELLANEOUS MALFORMATIONS (M) AND SINGLE-GENE TRAITS

THE RANGE OF MALFORMATIONS IN THE GROUP

In any listing of malformations the classifier is left with a miscellaneous group. In spite of a fairly elaborate system of grouping, 193 cases had to be left in this category. It includes the conditions reported only as affecting the eyes and ears and a number of single-gene traits, and, as will be seen from Table 15.1, by far the largest group is one which includes " atresia ", " stenosis " or absence of the external auditory meatuses.

In setting out that table there have been listed separately (*a*) all cases or groups of cases where any of the parents were related, (*b*) conditions where two or more cases of the same condition occurred and (*c*) single cases of some particular interest. In the " other " group no parents were related, there were no cases likely to be due to single-gene mutations and no more than one case of the type was reported.

It is convenient in this chapter to consider briefly the single-gene traits and one or two other malformations of some specific interest. To present a balanced picture in the discussions, information on all cases of the same type is considered together, even if not all examples were classified in the M group.

TRAITS DUE TO SINGLE-GENE MUTATIONS

On the basis of present understanding of human genetics certain types of cases determined by single-gene mutations would be expected to be found in the cases reported, although many single-gene traits would not be recognized in young infants. These will be considered seriatim.

Traits probably invariably determined by single-gene mutations

Defects probably due to recessive genes. As may be seen from Table 15.1, it is considered that albinism, epidermolysis bullosa, collodion foetus, amyotonia congenita and fibrocystic disease probably come into this category. In addition to the three cases of fibrocystic disease noted in this table, there were also five cases classified in E3.

Defects where a proportion of the cases reported are probably due to single recessive genes

Anophthalmia or microphthalmia. The anophthalmia/microphthalmia complex is sometimes caused by a single recessive gene and of the 16 cases where this was the only defect recorded three had consanguineous parents. Of the 20 cases where this defect occurred in cases in the N group, only one had related parents (Manila, Group N, No. 20) and this was not one of the cases with harelip and/or cleft palate. It seems reasonable to suppose that a majority of the cases where the primary defect is not failure of the fronto-nasal process are so determined.

The syndrome of agenesis of the abdominal wall and malformations of the urogenital tract. This syndrome, well reviewed by Mathieu et al. (1953), has been reported in sibs and the writers have seen two such families. In the M group there were seven cases, including two with consanguineous parents. None of the five very similar cases in the N group had related parents.

Some congenital cataracts are due to single recessive genes but the majority do not appear to be so caused. Cases of bilateral cystic ovaries and congenital corneal dystrophies are also sometimes recessive gene traits. Some of the " intersex " cases in the L group may have been of recessive adrenal virilism in females. There have been sibships with normal parents where more than one case of Pierre Robin syndrome occurred and these have been attributed to recessive mutations, but most of the mandibulofacial dysostoses appear to be due to irregularly manifest dominant genes. It has been suggested that the uncommon condition arthrogryphosis multiplex is also determined by recessive genes although the evidence is minimal. In addition to the four cases in the M group there were two cases in the N group, although the diagnosis in one of the two cases may be doubted. One of the N group cases had related parents.

Syndromes determined by single recessive genes but not recognizable as so caused

Probably the majority of recessive genes having visible homozygous effects in man are extremely

uncommon and affected individuals are seen so rarely that the origin of their malformed development is not recognized. It might be expected that some such cases would occur among the births in the study. It might also be expected that in a considerable proportion of these cases the parents would be related (the frequency of consanguinity and the gene frequency having an inverse relationship), but there is nothing suggestive of this in the cases in Table 15.1. It has to be remembered that the over-all frequency of consanguinity would determine its occurrence " by chance " in the parents of some malformed children.

Over-all it might be estimated that there were in the study some 30-40 malformations of the various types mentioned above which were attributable to homozygosity for single recessive genes.

Malformations due to dominant genes

Achondroplasia. As noted in section 13, the evidence suggests that about half of the 18 cases in the K and N groups cases shown as achondroplasia or chondrodystrophy were of the single dominant gene type of achondroplasia, as were the pair of male twins reported from Melbourne 2.

Osteogenesis imperfecta. It must be assumed that the 11 cases reported in K3 (section 13) were due to dominant genes and it may be surmised that some of the cases in the N group vaguely described as multiple skeletal malformations, etc., were really cases of this condition.

The mandibulo-facial dysostoses. As already noted, there is one case of this type in Table 15.1 and one in the N group. There were probably some cases of this condition in the cleft palate (G3) group. Most of these cases are probably due to irregularly expressed dominant genes.

Arachnodactyly. Diagnosis of arachnodactyly at birth and a decision as to whether this can be equated with Marfan's syndrome is by no means easy. In addition to the case listed in Table 15.1 whose parents were related, there were four cases where one of the malformations was called arachnodactyly in the N group born to unrelated parents. However, there must be some doubt as to whether this simply meant that the child had long digits.

Other conditions where single dominant genes probably made a contribution to cases. As noted in section 13, dominant genes probably determined some of the cases of polydactyly, syndactyly and other limb malformations but it is impossible to assess with any confidence what proportion of cases. Perhaps, to speculate, the proportion might be as high as 10% of the 756 cases in the J group.

There may be odd cases in other groups determined by dominant genes of this type so that over-all it seems likely that at least 100 of all the malformations reported in the study were so caused.

Finally, it has to be remembered that if there are dominant gene traits that are invariably lethal, in the genetic sense of causing early death or complete infertility, then they would never be recognized, and it may be that some malformations probably occurring with frequencies of the order of 1/50 000 to 1/100 000 in a population of births are so determined.

Malformations due to sex-linked genes

Probably the male in Table 15.1 affected by ectodermal dysplasia had the sex-linked type of this disorder, but there do not appear to be any other cases reported in the whole study individually identifiable as so caused. However, it seems very likely that, as noted in sections 4 and 7, some of the cases of hydrocephalus without spina bifida (B3) and some of the cases of imperforate anus (E2) were so caused. It may also be suspected that there is also a contribution both to tracheo-oesophageal fistula and to exomphalos where the male preponderance of cases is so marked.

If we assumed all the male excess of cases of anal atresia (E2) and exomphalos (E4) to be determined by sex-linked genes (an assumption difficult to defend), then we should arrive at an estimate of 33 cases in these categories due to sex-linked genes.

Total contribution of monofactorial traits

In all then, it seems likely that in between 100 and 200 of the 5430 malformed children in the study (5290 in single births and 140 in multiple births) their condition was due to single-gene mutations. As from other evidence we know that about 1% of those born alive suffer, or will suffer, from single-gene traits (Stevenson, 1959) it is clear that only a small proportion of those affected are recognized or recognizable at birth.

MALFORMATIONS IN THE M GROUP WHERE THE GENETICAL CONTRIBUTION, IF ANY, IS UNLIKELY TO BE MONOFACTORIAL

Abnormalities of external ears and external auditory meatuses

It is convenient to consider here the information from all the arbitrary malformation groups which

related to malformations of the ears. All except two very severe cases, where no mention was made of any atresia or stenosis of external auditory meatuses and there were no other malformations, were classed as " minor ". Where the sole malformation was of the ears and included mention of stenosis or occlusion of the meatuses the malformations have been placed in the M group. In addition there were many cases where ear malformations with or without meatal atresia occurred as one of several malformations and so were classified in the N group.

The cases classified as " minor " must in many instances represent subjective decisions of reporters because ears vary so much in shape that it is impossible to define with confidence the range of normality. This is not surprising in view of the number of contributing elements to the auricle and the complexity of their fusion. Many of the cases reported were termed " accessory auricles ", " abnormal ears ", " small ears " or " large ears " and there was no mention of " prehelicine pits " or " lobular pits " which are, in fact, quite common. In some of these cases and in others not reported at all there may have been deformities of the meatuses. Unless all newborns are examined by auroscope some atresias are bound to be missed.

The numbers of the cases of these various types may be seen in Table 15.2. Included in this table also are cases of the " synotia " syndrome, where the ears are low down in the neck and there is usually microstomia and severe dysplasia of the mandible. Most of the latter were classed to the N group, and again it is difficult for the physician to decide which cases should be so classed. Minor degrees of the condition are often identified among people met casually by any observant physician, but superficially they are not always easy to distinguish from the mandibulo-facial dysostoses. There has had to be a certain amount of interpretation of the very varying descriptions given of these cases. This difficulty was no less when translation from another language or " medical Latin " was necessary.

Of the 49 with atresia of the external auditory meatus, 43 left hospital alive so that, bearing in mind that some cases must be missed, about 1/10 000 appears to be a minimum frequency in living children. However, only about 10 of these cases were bilateral (the uncertainty is because in some cases it is not clear from the report whether the cases were unilateral or bilateral). It should, however, be remembered that in a number of cases thought to be unilateral it is found later that there is stenosis of the other meatus.

It is of importance that these cases should be recognized early as plastic surgery is proving increasingly successful in restoring hearing. The majority of cases prove to have a functioning middle ear and an intact internal ear.

It will be noted from Table 15.2 that there were no consanguineous parents of children with any of these ear deformities in the M group.

Sirenomelia

Sirenomelia or sympodia is an uncommon malformation. In all, five cases (four from the N group) were reported, or about 1 in 100 000. In these cases the sex is often indeterminate in that there may be no genitalia. The whole or part of the large bowel is usually absent and there are commonly also internal genito-urinary tract anomalies. Two of these cases were reported from Manila.

Other malformations

As will be seen from Table 15.1, remembering that in the 33 cases in the " other " group only one case of each defect is represented, the malformations listed all occur with very low frequencies (the denominator for any frequency being 416 695 single births). Apart from the case of Turner's syndrome (NFS) there are no cases identifiable as being due to chromosomal aberrations. It should be remembered that nearly 1 % of births probably have chromosomal aberrations although only a fraction are recognized, so that there were probably about 4000 so characterized in the study (these would include the cases of Down's syndrome). Finally, many of these M cases would probably have had to be classified as N or multiple if they had come to autopsy.

TABLE 15.1

NUMBERS OF SPECIFIED TYPES OF CASES IN THE M GROUP IN SINGLE BIRTHS

Type	Malformation	LBA	LBD & SB	M	F	NR	T	Number with related parents
Probably all cases due to autosomal recessive gene mutations	Albinism	2	0	2	0	0	2	0
	Epidermolysis bullosa	3	1	1	3	0	4	1
	" Collodion foetus "	1	0	0	1	0	1	0
	Amyotonia congenita	2	0	1	1	0	2	0
	Fibrocystic disease	3	0	1	2	0	3	0
Probably due to a sex-linked recessive gene	Ectodermal dysplasia	1	0	1	0	0	1	0
Most cases probably due to autosomal recessive genes	Anophthalmia or microphthalmia	14	2	7	9	0	16	3
	Agenesis-of-abdominal-wall syndrome	6	1	4	3	0	7	2
Possibly some cases due to single autosomal recessive genes	Cataract	7	1	4	4	0	8	0
	Other eye defects (mostly corneal)	7	2	6	3	0	9	2
Defects where some parents are related but there is no reason to suppose that defects are due to recessive genes	Marfan's syndrome	0	1	1	0	0	1	1
	" Massive thyroid tumour "	0	1	1	0	0	1	1
	Malformations of nose and nostrils	3	4	2	5	0	7	1
	Failure of midline fusion of mandible	0	1	0	1	0	1	1
	Epigastric hernia	3	0	1	2	0	3	1
	" Monster "	0	3	1	2	0	3	1
Defects where no parents were related and there is no reliable knowledge about the nature or degree of any genetical contribution to etiology	Absence or stenosis of external auditory meatuses	37	1	22	16	0	38	0
	Abnormal ears without stenosis of meatuses	3	1	1	3	0	4	0
	Agenesis of lungs	0	3	1	2	0	3	0
	Absence of specific muscles	5	0	3	2	0	5	0
	Absence of face	0	2	0	2	0	2	0
	Arthrogryphosis multiplex	2	2	3	1	0	4	0
	Craniomalacia	2	0	2	0	0	2	0
	Sirenomelia	0	1	0	0	1	1	0
	Synotia syndrome	0	1	0	1	0	1	0
	Hypoplasia of mandible (respiratory obstruction)	0	1	0	1	0	1	0
	Agenesis of skin	3	0	2	1	0	3	0
	Other skin conditions	1	2	1	2	0	3	0
	Thyroid enlargements, cysts, etc.	5	0	3	2	0	5	0
	Teratomas and tumours (various)	4	4	4	4	0	8	0
	Turner's syndrome	0	1	0	1	0	1	0
	Webbed neck	0	1	0	1	0	1	0
	Situs inversus totalis	2	2	3	1	0	4	0
	Cystic lung	1	1	2	0	0	2	0
	Choanal atresia	1	2	1	2	0	3	0
	Other	14	19	19	14	0	33	0
	Total	132	61	100	92	1	193	14

TABLE 15.2

ABNORMALITIES OF EARS IN M, N AND MINOR GROUPS IN SINGLE BIRTHS

Group in which recorded	Malformations of external ears; no mention of meatal defect			" Atresia ", stenosis or " absence " of external auditory meatuses			" Synotia " syndrome		
	M	F	T	M	F	T	M	F	T
M	1	3	4	22	16	38	0	1	1
N	19	21	40	5	6	11	3	2	5
Minor	172	141	313	0	0	0	0	0	0
Total	192	165	357	27	22	49	3	3	6
Grand total: M = 222; F = 190; T = 402.									